

Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language

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Sublingual immunotherapy (SLIT) is increasingly used worldwide. Despite its safety being well ascertained, there is no universally accepted system to grade and classify its adverse events (AEs). According to the literature, it seems reasonable to classify and grade systemic side effects by using the previously published World Allergy Organization recommendations. On the other hand, local side effects are the most frequent with SLIT, sometimes leading to its discontinuation. Therefore grading of the severity of local side effects was perceived as necessary for the purpose of uniform reporting, classification, and quantification of this aspect. A World Allergy Organization Taskforce, after examining the available literature and the postmarketing surveillance data, proposed a clinically based grading of the severity of local AEs caused by SLIT. The use of the Medical Dictionary for Regulatory Activities nomenclature for AEs was also included in this context. The proposed grading

system for SLIT-induced local reactions is expected to improve and harmonize surveillance and reporting of the safety of SLIT. (J Allergy Clin Immunol 2013;132:93-8.)

Key words: Sublingual immunotherapy, safety, local side effects, grading

Sublingual immunotherapy (SLIT) was first described in a double-blind randomized trial in 1986,¹ with the primary rationale of making immunotherapy safer and more convenient for the patient based on the observation that severe and even fatal adverse events (AEs) can occur with subcutaneous immunotherapy (SCIT).² SLIT has gradually been accepted in clinical practice as a viable alternative to SCIT,^{3,4} especially in Europe, Latin America, and other parts of the world. It is not US Food and Drug Administration approved for use in the United States.⁵

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Abbreviations used

AE:	Adverse event
MedDRA:	Medical Dictionary for Regulatory Activities
RCT:	Randomized controlled trial
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
WAO:	World Allergy Organization

There are more than 60 randomized double-blind, placebo-controlled trials, several systematic reviews of such trials,⁶⁻¹³ and a World Allergy Organization (WAO) position paper¹⁴ about SLIT. The safety profile of SLIT is superior to that of SCIT¹⁵; no fatalities have been reported, and severe systemic reactions are rare. The rate of AEs after SLIT is variable in the reported studies, but local AEs are predominant. More importantly, the report and description of such reactions are less than ideal, making it difficult to compare adverse reactions among studies, to identify risk factors, and to recommend appropriate action to take when a reaction occurs. Therefore a uniform grading system of AEs associated with SLIT, especially of local reactions, is necessary. This is appropriate because the WAO and other regional organizations recently approved a grading system for systemic adverse reactions to SCIT.¹⁶ The main advantages of using a widely agreed upon grading system in SLIT are (1) uniformity in reporting and comparing the safety of extracts, doses, and regimens; (2) improved epidemiologic knowledge on the safety of SLIT; (3) increased value of the postmarketing surveillance studies; (4) the possibility of identifying risk factors for AEs; and (5) provision of guidelines to doctors and patients on how to respond to a particular AE (ie, to continue, adjust, or stop treatment).

This document was based on randomized double-blind, placebo-controlled trials published in English and mentioned in the WAO position paper,¹⁴ studies with the same characteristics, postmarketing surveys, and case reports published up to December 2011.

ADVERSE REACTIONS ASSOCIATED WITH SLIT

To date, the safety profile of SLIT has been overall favorable. Systemic side effects (rhinitis, asthma, urticaria, angioedema, and hypotension) make up a minority of the adverse reactions because local reactions (oropharyngeal or gastrointestinal) are most frequently reported. Table I reports local AEs, as described in the literature, plus their coding according to the Medical Dictionary for Regulatory Activities (MedDRA)¹⁷ for reporting AEs. In this system AEs are hierarchically classified in 5 levels of detail, starting from the more general (system organ class) to the more specific (lowest level term). Each level better details the AEs and terminology of the previous levels. For example, Table I shows the 2 more detailed classification levels with the associated codes.

The current knowledge of adverse reactions caused by SLIT is based on randomized controlled trials (RCTs), postmarketing surveys, and case reports.

Randomized controlled studies

The safety of SLIT in RCTs is reviewed in the 2009 WAO position paper¹⁴ and in other reviews.^{15,18,19} André et al¹⁸ examined 8 trials performed with vaccines from a single manufacturer

involving 690 subjects (347 receiving active treatment plus 343 receiving placebo), of whom 218 were children aged 5 to 16 years (103 receiving active treatment plus 115 receiving placebo). Systemic reactions were mild, and the incidence did not differ in the active versus placebo groups. The oral and gastrointestinal side effects were more frequent with SLIT, with a similar rate in adults and children. Another review¹⁵ examined the safety of SLIT in the studies available up to October 2005. There were 1,047 adverse reactions from a total of 386,149 doses, which is 2.7 per 1,000 doses in 41 studies with sufficient information to analyze. The occurrence of severe reactions was 0.096 per 1,000 doses in studies that specified the severity of the reactions. Overall, 14 serious AEs were considered most likely treatment related (0.033/1,000 doses). In another review the occurrence of AEs was evaluated according to the SLIT dose, which was expressed as the ratio of SLIT and the equivalent SCIT.¹⁹ This review concluded that oral side effects were more frequent with low doses of allergen (<50 times the corresponding SCIT dose) than with higher doses. On the contrary, gastrointestinal complaints (nausea, upper abdominal pain, and vomiting) occurred more frequently with higher doses. However, this study is of limited value because the dichotomous distinction between high and low doses is totally arbitrary and has no experimental basis. More detailed information on local side effects has been reported in recent large trials (>200 patients) performed with grass extracts (Table II).²⁰⁻²⁷ The overall occurrence of systemic side effects is similar between the placebo and active groups in most studies. Oral side effects are quite frequent and invariably occur in more than 50% of patients receiving active SLIT, but their duration generally does not exceed 10 days, and discontinuation because of side effects is almost always less than 5%. Also, serious AEs reported in these trials are rare and usually not related to treatment. Of note, the occurrence and severity of AEs gradually decrease in the subsequent years of treatment, as reported in some follow-up assessment of previous trials.²⁸⁻³⁰

Postmarketing surveys and case reports

There are numerous SLIT postmarketing surveys³¹⁻⁴⁰ for both adult and pediatric subjects, some involving children younger than 5 years. These surveys are summarized in Table III, and show that the overall occurrence of AEs is lower in postmarketing surveys than in RCTs; this holds true especially for local AEs. This is probably the result of many events being judged as minimal by patients and not being reported.^{32,35,40} Where a more rigorous recording methodology is used (as happens in RCTs), the occurrence of AEs in patients approximates 50%. The majority of AEs in postmarketing studies are reported as oral, mild, and self-limiting, and the rate is less than 10 per 1,000 doses.

There have been, until December 2011, 6 case reports⁴¹⁻⁴⁵ of SLIT-induced systemic reactions that have been of a severity to be categorized as anaphylaxis.⁴⁶ Five occurred with standardized extracts and 1 with a mixture of 4 standardized and 2 nonstandardized extracts. One case was associated with the inadvertent administration of an overdose. An additional case of severe asthma after SLIT has been described.⁴⁷ Numbers were too small to permit firm conclusions with regard to risk factors for severe systemic reactions. Five of 6 patients were female, all were adolescents or young adults, 5 of 6 had a history of asthma, and 2 had a previous history of severe reactions to SCIT.

One potential approach as a result of these reports is to consider administering the first dose or doses of SLIT under medical

TABLE I. Description of local side effects related to SLIT (MedDRA 14.1)

	Local side effect	MedDRA preferred term	MedDRA code	MedDRA low-level term
Mouth/ear	Altered taste perception	Dysgeusia	10013911	Taste alteration
	Itching of lips	Oral pruritus	10052894	Itching of mouth
	Swelling of lips	Swelling of lips	10024570	Swelling of lips
	Itching of oral mucosa	Oral pruritus	10052894	Itching of mouth
	Swelling of oral mucosa	Mucosal edema	10030111	Mucosal swelling
	Itching of ears	Ear pruritus	10052138	Ear pruritus
	Swelling of tongue	Swollen tongue	10042727	Swelling of tongue, nonspecific
	Glossodynia	Glossodynia	10018388	Glossodynia
	Mouth ulcer	Mouth ulceration	10028034	Mouth ulcer
	Tongue ulcer	Tongue ulceration	10043991	Tongue ulceration
	Throat irritation	Throat irritation	10043521	Throat irritation
	Uvular edema	Pharyngeal edema	10034829	Pharyngeal edema
Upper gastrointestinal	Nausea	Nausea	10028813	Nausea
	Stomach ache	Abdominal pain, upper	10000087	Stomach ache
	Vomiting	Vomiting	10047700	Vomiting
Lower gastrointestinal	Abdominal pain	Abdominal pain	10000081	Abdominal pain
	Diarrhea	Diarrhea	10012735	Diarrhea

supervision. Another is that previous systemic reactions to SCIT have to be taken into account when initiating SLIT. Finally, it is mandatory to carefully instruct patients in the use of SLIT, as for any medication, to avoid accidental overdose and to minimize the risk of side effects.

GENERAL CONSIDERATIONS ON THE SIDE EFFECTS OF SLIT

SCIT can cause a variety of side effects or AEs, ranging from a local wheal-and-flare reaction at the site of the injection to anaphylaxis, with rare reports of deaths. The majority of the reactions are immediate (ie, occurring within 30 minutes) and therefore are IgE mediated; delayed reactions are also described. Local reactions that occur at the site of the allergen injection are common, expected, rarely bothersome,⁴⁸ and therefore not often reported. Other than systemic reactions, Mueller's classification⁴⁹ for adverse reactions to SCIT includes only large local reactions with a diameter of greater than 10 cm. In contrast, oropharyngeal or gastrointestinal reactions represent the majority of adverse reactions reported with SLIT, often leading to discontinuation of treatment and therefore necessitating a separate grading system. Another difference between SCIT and SLIT is that SLIT is self-administered, and thus many side effects are probably not reported or documented.

Local reactions associated with SLIT primarily occur in the mouth, the site of administration of the allergen vaccine. SLIT also is associated with lower gastrointestinal symptoms. A list of local signs and symptoms associated with SLIT administration is summarized in Table I. Reactions involving the lower digestive tract, such as diarrhea or abdominal discomfort, could be part of a "systemic" reaction, but in general, such reactions are classified as local.^{19,36,37} However, in some postmarketing surveys abdominal pain and diarrhea are included as systemic side effects.³¹⁻³⁶ We suggest that lower gastrointestinal tract reactions are local, unless they occur with other systemic manifestations, in which case they are classified as systemic reactions. The relationship between allergen dose and side effects is not clear because of the small sample size in many of the controlled studies. This is especially true for systemic AEs. However, 2 RCT

dose-effect safety studies with grass tablets^{50,51} showed a dose-response for systemic effects, with severe events reported only in the higher-dose groups, although there were no reported gastrointestinal side effects in these studies or in a safety study in children undergoing grass tablet SLIT.⁵² Gastrointestinal side effects were dose related in a review article¹⁹; that is, there was an increase as doses were escalated. However, a maximum tolerated dose is difficult to define for SLIT because dosages exceeding 1,000 times that given for SCIT or without up dosing have been administered without severe reactions.^{52,53} Many local AEs, especially those involving the oral pharynx, tend to disappear with subsequent doses. Finally, in many studies there is no up dosing phase, and the treatment is started with the maintenance dose. Such treatment does not increase the incidence of side effects.^{22,23,53}

PROPOSAL FOR A GRADING SYSTEM

The WAO grading of the systemic side effects associated with SCIT was written by a WAO panel of experts and endorsed by several scientific societies. Because the administration of any allergen, regardless of the administration route, can cause systemic adverse effects (including ocular symptoms, asthma, and urticaria), adopting the aforementioned classification for systemic side effects is adequate for SLIT.¹⁶

A similar grading system is also necessary for the local side effects of SLIT because they most commonly occur in clinical practice and their severity, persistence, or both can result in discontinuation of SLIT. With SLIT, the severity of local side effects has been assessed in different and arbitrary ways across various clinical trials. There are no objective parameters, such as changes in FEV₁ or blood pressure, to quantify the severity of the local AE; therefore a certain degree of subjectivity is unavoidable in grading these reactions. In general, the severity of local side effects depends on the signs and symptoms and their duration, keeping in mind that local side effects of SLIT tend to disappear after the initial doses. Another aspect to consider is whether a local side effect is sufficiently severe to cause discontinuation of SLIT, either because of single-event severity or duration or persistence with repeated dosing of local reactions that ultimately become intolerable. Thus if a patient has low-level local

TABLE II. Side effects in large randomized placebo-controlled trials with grass extracts performed in subjects with rhinoconjunctivitis (with/without asthma)

Reference	Age range (y)	Patients A/P	Updosing phase	Formulation	Duration	Manufacturer	Safety: Main results	Discontinued because of AEs
Durham et al, 2006 ²⁰	18-66	569/286, 3 doses	None	Tablets	6 mo	ALK-Abelló	Fifty-three percent of patients had AEs, mostly in the mouth. Six had SAEs. Duration of mouth AEs was 4-10 d.	Two percent of patients receiving SLIT withdrew because of AEs.
Dahl et al, 2006 ²¹	23-35	316/318	None	Tablets	6 mo	ALK-Abelló	Eighty-four percent of patients receiving SLIT and 64% of patients receiving placebo had AEs. There were more than 80 local SAEs in 5% of the active group and 7% of the placebo group. Eighty-five percent of the AEs were local.	Four percent of patients receiving SLIT withdrew because of AEs.
Didier et al, 2007 ²²	25-47	472/156, 3 doses	5 d	Tablets	6 mo	Stallergenes	Sixty-four percent of patients receiving SLIT and 48% of patients receiving placebo had AEs that were mostly local. SAEs occurred in 6% of the active group and 2% of the placebo group. Duration of local AEs was 5-11 d.	Five percent of patients receiving SLIT discontinued because of AEs.
Wahn et al, 2009 ²³	4-17	139/139	3 d	Tablets	8 mo	Stallergenes	Eighty-five percent of patients receiving SLIT and 82% of patients receiving placebo had AEs. Five SAEs were not related to treatment.	Five percent of patients receiving SLIT discontinued because of AEs.
Ott et al, 2009 ²⁴	20-50	142/67	1 d	Solution	5 y, 4 seasons	Stallergenes	Sixty-nine percent of patients receiving SLIT and 62% of patients receiving placebo had AEs. SAEs occurred in 7.5% of patients and were not related to SLIT.	Three percent of patients receiving SLIT discontinued because of related AEs.
Bufe et al, 2009 ²⁵	5-16	126/127	None	Tablets	6 mo	ALK-Abelló	Eighty-seven percent of patients receiving SLIT and 83% of patients receiving placebo had AEs. SAEs occurred in 4 patients and were not related to SLIT.	Four percent of patients discontinued because of SLIT-related AEs.
Nelson et al, 2011 ²⁷	18-63	213/225	None	Tablets	6 mo	Schering-Plough	Most patients receiving SLIT (72.8%) and some patients receiving placebo (27.6%) had AEs. Ninety-eight percent were mild to moderate in severity. Duration of local AEs was 1-7 d.	Of patients receiving SLIT, 5.2 discontinued because of side effects.
Blais et al, 2011 ²⁶	6-18	175/179	None	Tablets	6 mo	Schering-Plough	Seventy percent of patients receiving SLIT and 25% of patients receiving placebo had AEs. Four percent of patients receiving SLIT had urticaria. Duration of local AEs was 1-2 d.	Seven percent of patients receiving SLIT discontinued because of side effects.

A/P, Active/placebo; SAE, severe adverse event.

symptoms that persist for greater than 10 days and require no treatment and the patient does not regard them as bothersome and wishes to continue SLIT, then the reaction is classified as mild. Troublesome symptoms that might or might not require treatment but not result in discontinuation are classified as moderate. In this context the definition of severe most appropriately resides with the decision of the patient, doctor, or both to discontinue SLIT. Table IV is the proposed grading system for local side effects from SLIT.

Each of the symptoms listed in the first column can appear alone or in combination after SLIT administration. If the symptoms are not troublesome and do not require symptomatic treatment (typically oral antihistamines, antiemetics, and spasmolytics), the local event is judged to be mild. A moderate local effect is distinguished mainly because it is troublesome (ie, interferes with the patient's usual daily activities, including sleep, and/or requires symptomatic treatment). It is tempting to include functional impairment, such as difficulty in swallowing,

TABLE III. Reported rates of AEs in postmarketing surveys

Reference	No. of patients	Age range (y)	Follow-up (y)	Total AEs (% of patients)	Total AEs/1000 doses	Local AEs (% of patients)
Di Rienzo et al, 1999 ³¹	268	2-15	3	3	0.083	7
Lombardi et al, 2001 ³²	198	18-65	3	5.5	0.5	1.5
Pajno et al, 2003 ³³	354	5-15	3-4	6	0.15	Not stated
Fiocchi et al, 2005 ³⁴	65	3-7	1	15	Not stated	6
Drachenberg et al, 2004 ³⁵	159	6-60	<1	6.3	Not stated	5
Agostinis et al, 2005 ³⁶	36	3-5	2	5	0.07	Not stated
Di Rienzo et al, 2005 ³⁷	128	3-5	2	5.6	0.2	1.5
Rodriguez-Pérez et al, 2008 ³⁸	43	8-20	1	11.6*	0.3	46
Agostinis et al, 2008 ³⁹	33	3-18	1	41	4.4	32
Lombardi et al, 2008 ⁴⁰	159	16-59	1	63	6.5	41

*Including systemic side effects only.

TABLE IV. Grading system for SLIT local AEs*

Symptom/sign (see Table I)	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Unknown severity
Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema	<ul style="list-style-type: none">• Not troublesomeAND• No symptomatic treatment requiredAND• No discontinuation of SLIT because of local side effects	<ul style="list-style-type: none">• TroublesomeOR• Requires symptomatic treatmentAND• No discontinuation of SLIT because of local side effects	<ul style="list-style-type: none">• Grade 2AND• SLIT discontinued because of local side effects	Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician.

Each local AE can be early (<30 minutes) or delayed.

*See Table I for the MedDRA code that applies to exactly report and describe the AE.

breathing, or dehydration caused by severe gastrointestinal side effects, in the definition of severe reactions. However, the challenge is the subjectivity of the reporting of these symptoms, which could result in a wide spectrum of local effects being classified as severe. Should such side effects be judged sufficiently severe by the patient in consultation with his or her physician, then inevitably, the treatment should be discontinued, and the side effect should be classified as severe. Thus any occurrence of local side effects that requires discontinuing SLIT should be judged as severe.

There is also a need to include the category of unknown severity, in which the treatment is discontinued apparently because of side effects but there is no clear description from the patient, physician, and/or a reliable witness as to the nature of the side effects experienced. Local reactions occurring hours after dosing occur infrequently, but they do occur. For this reason, a distinction between early and delayed local side effects is included for descriptive purposes. An arbitrary time of 30 minutes is the point that distinguishes early from late side effects, as occur with SCIT.

CONCLUDING REMARKS

Uniform practice procedures, definitions, and classifications for the side effects of specific immunotherapy are recognized as necessary.^{14,54-57} A universally accepted classification and grading of SLIT side effects is important because local side effects associated with SLIT account for more than 80% of the adverse reactions from this form of treatment. Such a grading system will allow comparisons among studies, identification of possible risk factors, and potential improvement of the safety of treatment. The grading system proposed herein is based on these considerations. Because detailed knowledge of the side effects is essential

to identify the possible risk factors and improve clinical practice,⁵⁸ all clinicians who prescribe SLIT should report all severe AEs and anaphylaxis occurring with SLIT to manufacturers, regulatory authorities, or both.

Because postmarketing safety surveillance is required for all marketed treatments, reports in the postmarketing phase represent an important tool in monitoring the safety and any required revision of the prescribing information. The classification and reporting methods are relatively standardized worldwide, but underreporting exists and results in limitations in these reports: incomplete data, poor-quality data, and difficulty in demonstrating a causal relationship between exposure and AEs. For these reasons, we also recommend that SLIT-induced adverse reactions be described and codified by using MedDRA (Table I),^{54,59} which is a clinically validated international medical terminology used by regulatory authorities in many countries.

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REFERENCES

1. Scadding G, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to dust mite. *Clin Allergy* 1986;16:483-91.
2. Windom HH, Lockey RF. An update on the safety of specific immunotherapy. *Curr Opin Allergy Clin Immunol* 2008;8:571-6.
3. Bousquet RF, Lockey RF, Malling RF, editors. World Health Organization position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;53(suppl):1-42.
4. Bousquet RF, Van Cauwenberge RF, editors. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 suppl):S146-50.

5. American Medical Association. Current procedural terminology (CPT) 2005 standard edition. Chicago: American Medical Association; 2005.
6. Wilson DR, Torres L, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Allergy* 2005;60:3-8.
7. Calamita Z, Saconato H, Pelà AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma. Systematic review of randomized clinical trials. *Allergy* 2006;61:1162-72.
8. Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008;133:599-609.
9. Penagos M, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006;97:141-8.
10. Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy* 2009;64:1570-9.
11. Di Bona D, Plaia A, Scafidi V, Leto-Barone MS, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2010;126:558-66.
12. Radulovic S, Calderon MA, Duncan W, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010;(8):CD002893.
13. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. *Cochrane Database Syst Rev* 2011;(6):CD007685.
14. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al, editors. WAO position paper on sublingual immunotherapy. *Allergy* 2009;64(suppl 91):1-15.
15. Cox L, Larenas-Linneman D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;117:1021-35.
16. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. *J Allergy Clin Immunol* 2010;125:569-74.
17. Medical Dictionary for Regulatory Activities (MedDRA). Maintenance support services and organization. Available at: <http://www.meddrasso.com/>. Accessed July 2012.
18. André C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000;121:229-34.
19. Gidaro GB, Frati F, Sensi L, Marcucci F, Incorvaia C, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy* 2005;35:565-71.
20. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass-allergen tablets: a randomised controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802-9.
21. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;118:434-40.
22. Didier A, Mallin HJ, Worm M, Horak F, Jäger S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338-45.
23. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5 grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;123:160-6.
24. Ott H, Sieber J, Brehler R, Fölster-Holst R, Kapp A, Klimek L, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 2009;64:179-86.
25. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009;123:167-73.
26. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011;127:64-71.
27. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;127:72-80.
28. Didier A, Worm M, Horak F, Sussman G, de Beaumont O, Le Gall M, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol* 2011;128:559-66.
29. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK. SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717-25.
30. Halken S, Agertoft L, Seidenberg J, Bauer CP, Payot F, Martin-Muñoz MF, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol* 2010;21:970-6.
31. Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in children. *Allergy* 1999;54:1110-3.
32. Lombardi C, Gargioni S, Melchiorre A, Passalacqua G. Safety of sublingual immunotherapy in adults: a post marketing surveillance study. *Allergy* 2001;56:889-92.
33. Pajno GB, Peroni DG, Vita D, Pietrobelli A, Parmiani S, Boner AL. Safety of Sublingual immunotherapy in children with asthma. *Paediatr Drugs* 2003;5:777-81.
34. Fiocchi A, Pajno G, La Grutta S, Pezzuto F, Incorvaia C, Sensi L, et al. Safety of SLIT in children aged 3 to 7 years. *Ann Allergy Asthma Immunol* 2005;95:254-8.
35. Drachenberg KJ, Urban E, Proll S, Woroniecki SR. Sublingual specific immunotherapy for adults and children: a post marketing survey. *Allergol Immunopathol* 2004;32:76-81.
36. Agostinis F, Tellarini L, Falagiani P, Canonica GW, Passalacqua G. Safety of SLIT in very young children. *Allergy* 2005;60:133.
37. Di Rienzo V, Minelli M, Musarra A, Sambugaro R, Pecora S, Canonica WG, et al. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy* 2005;35:560-4.
38. Rodríguez-Pérez N, Ambriz-Moreno Mde J, Canonica GW, Penagos M. Frequency of acute systemic reactions in patients with allergic rhinitis and asthma treated with sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2008;101:304-10.
39. Agostinis F, Foglia C, Landi M, Cottini M, Lombardi C, Canonica GW, et al. The safety of sublingual immunotherapy with one or multiple pollen allergens in children. *Allergy* 2008;63:1637-9.
40. Lombardi C, Gargioni S, Cottini M, Canonica GW, Passalacqua G. The safety of sublingual immunotherapy with one or more allergens in adults. *Allergy* 2008;63:375-6.
41. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy* 2006;61:1236-7.
42. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 2007;62:567-8.
43. De Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009;64:963-4.
44. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy* 2008;63:374.
45. Dunskey E, Goldstein MF, Dvorin MJ, Belecanech G. Anaphylaxis due to sublingual immunotherapy. *Allergy* 2006;61:1235.
46. Simons FER, Arduoso L, Bilò B, El Gamal Y, Ledford DK, Ring J, et al. Anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;127:587-93.
47. Cochard MM, Eigenmann PA. Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy. *J Allergy Clin Immunol* 2009;124:378-9.
48. Coop CA, Tankersley MS. Patient perceptions regarding local reactions from allergen immunotherapy injections. *Ann Allergy Asthma Immunol* 2008;101:96-100.
49. Position paper: immunotherapy. (EAACI) The European Academy of Allergology and Clinical Immunology. *Allergy* 1993;48:7-35.
50. Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. *Allergy* 2006;61:181-4.
51. Larsen H, Poulsen LK, Melac M, Combebias A, Andre C, Mallin HJ. Safety and tolerability of grass pollen tablets in sublingual immunotherapy – a phase-I study. *Allergy* 2006;61:1173-6.
52. Ibanez MD, Kaiser F, Knecht R, Armentia A, Schopfer H, Tholstrup B, et al. Safety of specific sublingual immunotherapy with SQ standardized grass allergen tablets in children. *Pediatr Allergy Immunol* 2007;18:516-22.
53. Rodriguez F, Boquete M, Ibanez MD, de la Torre-Martinez F, Tabar AI. Once daily sublingual immunotherapy without up dosing—a new treatment schedule. *Int Arch Allergy Immunol* 2006;140:321-6.
54. Sabin BR, Saltoun CA, Avila PC. Advances in upper airway diseases and allergen immunotherapy. *J Allergy Clin Immunol* 2011;127:342-50.
55. Peden DB, Bush RK. Advances in environmental and occupational respiratory disease in 2010. *J Allergy Clin Immunol* 2011;127:696-700.
56. Nelson HS. Subcutaneous immunotherapy. *J Allergy Clin Immunol* 2011;128:907.
57. Casale TB, Stokes JR. Future forms of immunotherapy. *J Allergy Clin Immunol* 2011;127:8-15.
58. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999;20:109-17.
59. Bousquet C, Lagier G, Lillo-Le Louet A, Le Beller C, Venot A, Jaulet MC. Appraisal of the MedDRA conceptual structure for describing and grouping adverse drug reactions. *Drug Saf* 2005;28:19-34.